SECTION 3— BIOLOGICAL TECHNOLOGY

Scope

Highlights

- Biotechnology has sustained a growth rate of doubling the base of knowledge every 18 months to 2 years. This trend appears to be accelerating in the human genome, multi-array sensor, and biomaterials areas.
- The economic engine for biotechnology is the non-military commercial sector, including medicine/health, agriculture/food processing, cosmetics, and transportation.
- Significant advances in biotechnology capabilities should be anticipated from developed nations and less-developed nations.

OVERVIEW

The rapid growth of biotechnology since 1970 has provided many items and systems that are useful to the civilian and the military sectors. These products and processes relate to improvements in human health by production of new pharmaceuticals, including antibiotics, vaccines, and performance sustainers. Sensors capable of detecting infectious agents, toxins, and chemical agents have been developed and miniaturized using insights provided by biotechnology. During the past decade, innovations in monitoring human performance, vigilance, and fitness for duty have emerged from the use of imaging systems that permit viewing brain activity on-line and correlating the electrophysiological activity of the brain with human performance. Advances in genetic engineering, molecular biology, and polymer chemistry have created new opportunities in the fabrication of electronic circuits, molecular motors, and structures having high strength and low weight. The shelf life and palatability of foods has been markedly improved by discoveries in biotechnology.

The rapid growth in all these areas has been accompanied by federal and private sector investment in the United States and other developed nations. Some of this advanced technology has been acquired by developing nations, including those hostile to U.S. interests. This section describes the developing biotechnologies anticipated to be realized in a 20-year frame. The roles of biological systems in the production of electrical energy are included in the Energy Technology section of the Militarily Critical Technologies List (MCTL).

The rate of economic growth of the biotechnology industry is the most rapid of all industrial sectors, and this reflects the perceived importance of this industry on product development, processes, and systems. Between 1996 and 1997, the market capitalization of this industry increased 60 percent—from $52 to $83 billion. The revenues increased 15 percent, and the sales increased 16 percent. The largest applications of medically related biotechnology were in the United States.

Each of the technology items identified in this section is being driven by broad requirements and applications. All are expected to develop a substantial set of non-military commercial applications and attendant manufacturing and support infrastructures. The industrial sectors supporting the biotechnology thrusts include health/medicine, pharmaceuticals, agriculture/food processing, and transportation.

In this section, the developing technologies have been categorized into four groups:

1. Human Performance Enhancement
2. Biological Sensors
3. Biomaterials and Nanofabrication
4. Individual and Group Protection

Table 3.0-1 provides a matrix of the 22 developing technologies and identifies where they are covered within the four technology areas.

Table 3.0-1. Listing of Developing Technologies and Concepts by Technology Group

	Technology Groups			
Developing Technology	**Human Performance Enhancement**	**Biological Sensors**	**Biomaterials and Nanofabrication**	**Individual and Group Protection**
A. Recognition/perception	X			
B. Memory	X			
C. Visual/auditory/olfactory	X			
D. Cognition	X			
E. Electrophysiological monitor and brain activity	X			
F. Brain imaging	X			
G. Human performance maximization	X			
H. Nanofabrication		X	X	
I. Sensors/molecular recognition		X		
J. Biomedical imaging and automation				X
K. Biomaterials		X	X	
L. Encapsulation		X		X
M. Human Genome Project	X			X
N. Pathogen Genome Project		X		X
O. Atomic Force Microscopy (AFM) and Nearfield Optical Scanning Microscopy (NSOM)		X	X	
P. Increased disease resistance				X
Q. Thin films [charged coupled device (CCD)]		X	X	
R. Microelectromechanical Systems (MEMS)		X	X	
S. Blood substitutes and biocompatible clotting matrices				X
T. Locator of persons				X
U. Water purification				X
V. Biomarkers for toxicant/stress exposure	X			X

High-value-added products requiring these technologies are in the pharmaceutical, food, and cosmetic arenas. The rapid progress currently seen in the Human Genome Project is likely to give rise to an explosion of new products affecting human health, performance, and disease resistance. New diagnostic procedures for disease susceptibility and anticipated life-span enhancement will emerge. Since the sequencing of the genome of bacteria, viruses, and fungi is progressing at a high rate and results are correlated with genomic data from the Human Genome Project, the genetics of disease susceptibility in various human populations will emerge. A current example is the finding in 1998 that resistance to Human Immunodeficiency Virus (HIV) in persons of European ancestry is associated with resistance to plague developed in these populations during the epidemics of the 14th to 17th centuries. The genetic factors responsible for virulence of certain bacteria, viruses. and fungi are currently being identified, and the pathogenicity islands (PAIs) are being mapped.

SECTION 3.1—HUMAN PERFORMANCE ENHANCEMENT

Highlights

- Selection of personnel for task suitability will become increasingly accurate and sensitive based on identification of specific biomarkers for toxicant susceptibility, stress, sustained performance.
- Performance monitoring and warning will enhance the ability of the military cohort to sustain and maximize mission goals of individuals and teams.

OVERVIEW

In the future, one of the most significant applications of emerging biotechnologies will be to enhance human performance by improving perception, information processing, decision-making, and task execution capabilities. Biotechnology can be used to increase these facets of human performance in three areas:

- **Physiological monitoring.** Psychological monitoring technologies, using miniaturized electrodes and data fusion systems that require low energy will detect and assess changes in cardiovascular and neurological processes in real-time to drive system adaptation.
- **Information display and control.** Information display and control technologies will present and organize information or control systems to optimize awareness, decision-making, workload, and reaction times.
- **Pharmacological intervention.** Pharmacological intervention technologies, such as drugs or environmental changes, will improve the physiological processes underlying human performance.

These areas will provide for the prescreening of personnel to determine genetic and non-genetic prognosticators that may indicate a susceptibility to stress and toxicants and for the analyses of paradigms for complex behaviors involving swarms and hives.

TECHNOLOGY DESCRIPTIONS

Physiological Monitoring

Technologies that can non-obtrusively measure core physiological processes are evolving. Applied research is successfully producing models that use those measures to reliably determine operator cognitive workload, vigilance, and fatigue to drive task allocation between the operator and the system or change information presentation to capitalize on available resources. The physiological parameters that may be correlated with functional performance changes include auditory and visually evoked potentials, broadband brain activity (e.g., using complex electroncephalographic output with an extended numbers of channels), eye movements, heart interbeat intervals, respiration rates, and blood oxygen levels. Imaging technologies, especially functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) using ^{15}O or ^{18}F labeled derivatives, and magnetoencephalography, can reveal brain areas that are active during specific tasks.

These technologies promise real-time analyses of performance for automation decisions or rapid screening tools for measuring job fitness. Interpretation of EEG-monitored brain wave patterns to indicate intended operator actions will occur on-line with near instantaneous reaction times and will allow the elimination of motor response errors (termed “brain activated control”). Technologies requiring physiological inputs, such as brain activated control, will capitalize on the development of remote (i.e., non-contact) sensors and analytical tools like fMRI. In addition, physiological changes could be inferred from changes in task accomplishment or loading using models of human performance. Monitoring of operator state for impending unconsciousness will serve to ensure safety by permitting the automatic transfer of operator control to the system computer.

The biochemical markers of acute exposure to stress include the enzymes glutathione S-transferases and cytochrome P450. Biomarkers that reveal longer term exposure to conditions that compromise function or lead to unacceptable risk for error in highly skilled individuals are also of critical importance. Recent advances in the behavioral sciences, neurophysiology, biochemistry, medical imaging, and ergonomics provide the opportunity for developing early physiological monitoring techniques to detect situations that will degrade human performance. The development of unobtrusive monitors for these early warning markers will increase the likelihood of effective performance and reduce the risk of failure.

Information Display and Control

In the realm of biotechnology, the presentation of information or the employment of control modalities can be designed to capitalize on specific interactions with human perceptual, cognitive, or motor systems. It can be expected that the human-machine interface will be incrementally transformed into an interactive fusion driven by changes in neurophysiological states.

The modeling of human information processing will be precise enough to design truly intuitive interfaces and to delineate the differences between computer and human information processing to optimize human-machine interactions and the allocation of mission functions. This improved understanding of mental processes will lead to enhanced situational awareness and decision-making by fundamentally changing the structuring of information interactions. Real-time monitoring of operator cognitive and perceptual resource consumption (i.e., workload) coupled with performance measures will tailor information formatting to sensory modality and the assignment of tasking between the human and machine. This will provide a set of new boundaries in human information processing tailored to the individual performer.

Pharmacological Intervention

The nature of the biological mechanism that allows a person to discriminate a subject cognitively from its background has been termed the “binding problem.” Currently, two fundamental theories address the binding problem:

- There exist nerve cells that store all the collective neural inputs for a solitary object through unique neurons (e.g., a cell that is used to recognize “grandmother”). Accordingly, different “grandmother cells” would be required for recognition of all items in long-term memory.
- There exist gamma phased 40-Hz circuits that are programmed to become activated when a target to be recognized appears. Sets of individual 40-Hz circuits may collectively comprise Hebbian circuits. If the memory is comprised of 40-Hz circuits, the introduction of selective 40-Hz signals from external sources may stimulate or suppress the memory system.

Evidence exists to support each of these physiological processes in different scenarios. The next decade is likely to see novel approaches to the design of pharmaceuticals that can enhance recognition speed and accuracy. Compounds, such as AMPAkines, that increase both working and long-term memory functions will significantly improve awareness, decision-making, and task execution under stress.

The sequencing of the entire human genome is expected to be complete by 2005. The genome will be characterized by rapid gene sequencers. One system in development prepares 400,000 bases per hour and analyzes about 8,000 bases per 16 hours. This system can determine the sequence of about 2 million bases per several months. A second strategy uses variants of mass spectrometry to sequence DNA. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry has proved to be an important tool in synthetic- and bio-polymer characterization. The molecular sizes that can be sequenced by this technique are limited in 1997 but the method currently has utility for determining mutation sites in DNA fragments. The information to be obtained from characterization of the human genome is likely to provide an understanding of performance, vigilance, and susceptibility to disease.

Classical gene therapy approaches allow new genes or functions to be introduced into cells or individuals to correct genetic disorders. While optimal vehicles for gene therapy still need to be developed, this limitation is likely to be solved in the foreseeable future, opening the way to many applications. In addition to correcting genetic defects, the same technology could be used to enhance performance or allow new capabilities. An extension of this

notion is the use of similar technological approaches to control specific genes—turning them on or off at particular times. As one example, many of the genes responsible for programmed cell death (apoptosis) have been identified. Selectively altering their expression could greatly extend the life of desired cells or help to prevent their premature death, and, in combination with use or expression of growth factors, make possible selective growth control and controlled tissue regeneration.

Combinatorial genomics has also recently been developed. Similar in concept to combinatorial chemistry, this technology shuffles portions of genes to give a vast number of new combinations, which are then screened for a desired function. Enhanced function, or even new functions, can be generated by repeating the cycle many times to "evolve" optimized recombinants in vitro.

Research characterizing the expression of specific genes has determined that several genes, most notably the cyclic AMP response element binding protein (CREB) gene, have products that enhance memory function in humans. The binding protein may be regulated by phosphorylation. As the human genome is further characterized, it is likely that other gene products will be associated with memory. Knowledge of the gene sequence can facilitate the development of drugs that interact with critical regions of the gene to increase production of proteins that enhance memory. Conversely, anti-sense molecules that effectively block proteins that diminish memory may be developed. The analyses of the genome of people with senile dementia or Huntington disease may reveal the existence of gene products that compromise memory.

Increasing knowledge about the hormonal and neurochemical basis of circadian rhythms and their role in memory, vigilance, decision-making, and other cognitive functions will lead to meaningful drug interventions. Under normal conditions, circadian rhythms are entrained to approximately 24 hours by the presence of a number of Zeitgebers (i.e., environmental events that provide the stimulus setting the biological clock), such as the occurrence of light and dark, that inhibit or permit the release of melatonin, a hormone produced by the pineal gland. Strategies that use melatonin to induce sleep or shift circadian rhythms to negate jet lag or block melatonin (e.g., bright light) or to sustain arousal will enhance performance during time zone transitions.

TIMELINE FOR TECHNOLOGY AVAILABILITY

Predicting when specific human performance enhancement technologies will be routinely available is difficult because gradations of capability will be introduced progressively. This notwithstanding, projections for the near, mid, and far term can be made with some confidence. Near term implies 3–5 years, midterm implies greater than 5 years but less than 10 years, and far term implies greater than 10 years. The application of perception and cognition research to the design of intuitive interfaces, automation, and decision-making will begin in the near term, some real-time, rudimentary physiological monitoring driving meaningful changes in task allocation will be available in the midterm, and true system fusion and, later, control of systems by thought will be available in the far term. Revolutionary changes in the human systems interface will appear at the end of the near term or in the midterm. Significant pharmacological interventions to manage fatigue will begin in the next few years, but drugs or gene products that will change memory, for example, will appear in the midterm.

ADDITIONAL DATA

Tables 3.1-1A and 3.1-1B present additional data on this developing critical technology area.

Table 3.1-1A. Human Performance Enhancement Militarily Critical Technologies

Technology	Developing Critical Technology Parameter	Critical Materials	Unique Test, Production, and Inspection Equipment
Miniaturized, non-obtrusive measures of eye movements; auditory- and visual-evoked potentials; EEG; cardiac interbeat interval; oxygen saturation	Drowsiness indicator; vigilance and fitness monitor; physiological indicators that predict decreased combat performance. Miniaturized auditory evolved potential in the 300-ms wave and visual in the 300–600 ms wave. Application ready in near term to midterm for evoked potential and eye movement.	Miniaturized sensors embedded in body cover or helmet; lightweight data fusion tools and energy-efficient signal transmissions.	None identified.
Functional MRI	Simulator training with fMRI correlates brain functional response to training to job criteria. Magnet level of 1.8 Tesla or higher.	Non-magnetic simulator system required to use MRI.	None identified.
Information display and control. Robust voice control of military systems; 3–D audio/visual displays; brain activated control of machine interfaces; haptic interfaces; HMDs	Interface-evoked potentials with human-machine interfaces and virtual reality projectors. Response times in 10 to 100 ms.	Integrated audio/visual/ haptic information presentation.	None identified.
Pharmacological interventions, including drugs that affect object recognition and improve memory functions and drugs that control arousal or sleep and produce circadian synchronization	Permits selective intervention in time-limited and reversible manner. Intervention is effective within minutes, and duration is hours. A sustained high performance level, including sleep/work cycles synchronized to work demands.	Drugs that bind or otherwise affect CREB or offer AMPAkines, functions.	None identified.
Biomarkers for early detection of genetic susceptibility to toxicants and stress	Rapid identification (in hours) of human genes affecting susceptibility to toxicants, to stress, and to disease. Includes genes for cytochrome P450, GST, acute phase proteins. Application ready near term to midterm.	None identified.	None identified.
Biomarkers for detection of environmental agents or conditions that adversely affect human performance	Detect body response to and insulate from toxicants that degrade human performance in either or both near term (minutes to hours) and long term (years). Glutathione transferases and cytochrome P450 are detector biomolecules. Application ready near term to midterm.	None identified.	None identified.

Table 3.1-1B. Human Performance Enhancement Militarily Critical Technologies

Technology	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
Miniaturized, non-obtrusive measures of eye movements; auditory- and visual-evoked potentials; EEG; cardiac interbeat interval; oxygen saturation	Signal-averaging miniaturization and data-sorting algorithms and programs.	Multiple commercial development centers include production line assessments in factories; determine effectiveness of medical care delivery (e.g., surgery); assess human monitor of chemical process production (petroleum industry); measure fitness of pilots and railway engineers; monitor patients.	Provides equivalent indicators of loss of vigilance and fitness and predicts decreased performance and readiness in industry and commerce.	Commercial applications drive technology in biomedical arena. Leading-edge R&D is commercial.	Ready access for the military. Some proprietary issues apply.	None identified.
Functional MRI	None identified.	Training centers for airline pilots and railway engineers; medical monitors for patient status.	Diagnosis of disease in patients. Training for high-skilled jobs.	None identified. Still in development.	Ready access.	None identified.
Information display and control. Robust voice control of military systems; 3–D audio/visual displays; brain activated control of machine interfaces; haptic interfaces; HMDs	Software for interfaces.	Biomedical applications in operating rooms for anesthesiology; precision machining of production processes involving toxic/ radioactive materials.	Decrease response time under stress; motor workload and tasking; enhance performance in variable shift work.	Commercial applications drive the technology.	Ready access.	None identified.
Pharmacological interventions, including drugs that affect object recognition and improve memory functions and drugs that control arousal or sleep and produce circadian synchronization	None identified.	Military will want to develop counter-measures for drugs that disrupt memory processes.	Training of people for complex tasks; treat learning disabilities (ADD).	The commercial and military world have complementary needs.	Ready access to drugs for learning enhancement.	None identified.

(Continued)

Table 3.1-1B. Human Performance Enhancement Militarily Critical Technologies (Continued)

Technology	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
Biomarkers for early detection of genetic susceptibility to toxicants and stress	Database of human genome.	The medical and pharmaceutical industry and the NIH fund 90 percent of this activity.	Liability assessment; biomedical diagnostics.	Commercial sector drives technology.	Ready access to human genome.	None identified.
Biomarkers for detection of environmental agents or conditions that adversely affect human performance	Database of correlative information.	Industrial hygiene; OSHA and industrial liability concerns have interest.	Improve safety of workplace and reduce liability.	Private sector and NIH are major supporters of technology development.	Ready access.	See Biomedical Section, Part III of MCTL. Ethic and privacy cultural issues involved.
Miniaturized, non-obtrusive measures of eye movements; auditory- and visual-evoked potentials; EEG; cardiac interbeat interval; oxygen saturation	Signal-averaging miniaturization and data-sorting algorithms and programs.	Multiple commercial development centers include production line assessments in factories; determine effectiveness of medical care delivery (e.g., surgery); assess human monitor of chemical process production (petroleum industry); measure fitness of pilots and railway engineers; monitor patients.	Provides equivalent indicators of loss of vigilance and fitness and predicts decreased performance and readiness in industry and commerce.	Commercial applications drive technology in biomedical arena. Leading-edge R&D is commercial.	Ready access for the military. Some proprie-tary issues apply.	None identified.

SECTION 3.2—BIOLOGICAL SENSORS

Highlights

- Biological multi-array sensors will permit rapid and accurate acquisition, storage, and assessment of data for biological, chemical, and mechanical signals.
- Biological sensors are anticipated to be more compact, energy efficient, and sensitive than non-biological units.

OVERVIEW

A sensor provides the interface through which a system can detect the state of a changing environment in real time. It can also provide information about the interaction between the environment and individuals. Appropriate sensors and data fusion systems serve to integrate operational systems in much the same way as the sensory nervous system in the body. This analogy has given impetus to the construction of multi-spectral [shark-electromagnetic detection; pigeons and ultraviolet (UV) detection; swine and canine odor detection] and non-traditional (abiotic "sensored" insects) sensors. Because of the integration of advances in optics, electronics, microfabrication technology, and molecular biochemistry biosensor technology is an area of rapid technological progress. Concepts that will result in improved field sensors by the year 2010 include gene probes, monoclonal and genetically engineered antibodies and other receptors, high-precision polymer molding, polymer liquid crystals, chemiluminescence, neuronal and protein DNA patterning, combinatorial chemistry, monolithic UV/visible/infrared (IR) laser light-emitting and -detecting surfaces, Microelectromechanical Systems (MEMS), charge coupled devices (CCDs), and neural networks.

At present and, in fact, in our entire history of chemical syntheses, it is estimated that less than one percent of all possible organic compounds have been synthesized. Combinatorial chemistry uses automated production and screening of thousands of compounds, typically for drug screening or for materials with novel electroconductive properties. The number of compounds that can be synthesized per day is now in the thousands, and the production size is growing. One method produces as many as 25,000 different substances on a 3-inch diameter substrate. The challenge of this technology is to develop methods that rapidly screen the newly synthesized materials for properties of interest. Technologies for large-scale screening remain to be developed.

Advances in synthesis and screening will lead to very small, lightweight, energy efficient biosensors capable of simultaneous analysis for multiple analytes. All sensors would be reduced to a card format and integrated into a single case. Individual sensors can be formatted with both the biodetection components and the optoelectronic sensing elements in micron-scale arrays. Microfluidics, data processing, data transmission/display elements, and electropower sources will be incorporated with the optical or electrochemical detector and the molecular or cellular biodetection components in a fully automated hand-held unit. For automated environmental monitoring, these units will be adaptable to a variety of platforms. Materials that have applications in display technology can be rapidly screened.

In 10–30 years, sensors and sensor suites will be "smart devices" that perform appropriate analyses, data fusion, and evaluation and then trigger an appropriate response.

Array sensors for enzymes, analytes, antigens, antibodies, receptors, and nucleic acid targets are available on chips containing not only the biocomponents but also the integrated circuitry to record the results. These arrays are supplied in the form of small disposable cassettes into which a sample of whole blood or any other biological fluid can be added. The "chip" will process the sample as required and move the processed material—through either capillary action or a small micropump—to the sites of analysis. The results could be read or telemetered to an off-site location for analysis and decisions regarding treatment and response.

Sensors provide data regarding materials and conditions in the surrounding environment.

The most recent approaches have focused on exploiting the high affinity binding of naturally occurring molecules to target materials of interest. The molecules include polynucleotides that recognize pathogenic genome sequences of B agents or human genomic material of interest, monoclonal and polyclonal antibodies that recognize surface molecules of B or C agents, and receptors that change conformation following exposure to B or C agents and generate an electronic or photonic signal.

TECHNOLOGY DESCRIPTIONS

Molecular Recognition Components

Arrays based on antibodies, nucleic acid sequences, or receptors are in production at the close of the 20th Century. Genomic sequencing of all known infectious disease organisms is in progress. Some regions of the bacterial genome appear to be common among organisms pathogenic to humans (e.g., pathogenicity islands). Such regions could be used in detecting pathogens on nucleic acid arrays or other type of DNA/RNA detection systems. In addition, using anti-sense gene technology, stopping the pathogenic activity of an organism by tying up this region of the pathogens genome may be possible.

Nucleic acid oligomer arrays for the detection of specific gene sequences have been produced on patterned surfaces. Similar arrays, for the sequencing of genes at very rapid rates to determine "viral load" and mutations, are being generated. Antibody and antigen arrays for detecting and quantifying antigens and antibodies that will permit the assay of several analytes simultaneously are in development.

This technology addresses real-world problems. Anthrax and other biological agents are normally present in particular environments. These agents vary in natural abundance as a function of geographical location, land use, season, and meteorological conditions. After a database has been established for natural abundance of each biological agent in a given setting, the multi-array sensor will inform the user when a threshold that requires action has been reached. This type of approach will be inexpensive, fast, and portable.

The application of receptors in analyses, as opposed to antibodies, is of great interest. Receptor- and antibody-based sensors are complementary and, in certain situations, may be useful together on an array. Antibodies provide information on mass, but not biological activity. Ligand binding to receptors provides information on biological activity, but not mass.

A Human Vital Systems Card is an example of an integrated biosensor and data fusion component. The devices use different technologies and perform different functions by measurement of parameters, such as pO_2, pCO_2, pH, glucose, creatinine, blood urea nitrogen, blood electrolytes, and other components that would indicate the state of the individual. These devices can use MEMS and/or nanofabrication technologies and be small enough to use either by being implanted under the skin or attached to the skin surface. Advances in non-invasive technologies will be required for this type of sensor.

Biological and Biomimetic Photon and Electron Transfer Materials

Bacterial Rhodopsin is a transmembrane protein of approximately 27 kilodaltons and is light-sensitive. When exposed to yellow light, it pumps a proton from the interior of the cell-membrane to the exterior through a photocyle. During this photocycle, it passes through several intermediate states with unique characteristics and life times. This protein could be faster than a Josephson Junction for switching and could operate at room temperature. It has potential for holography, information storage and retrieval at the molecular level and molecular computing. An artificial retina using a light-sensitive material, such as bacterial rhodopsin or one of the porphyrin containing dyes on a chip, has been produced in prototype form. Such a device could be implanted in the eye and electrically connected to the optical nerve. Although the signals sent to the brain will not be the same as those in normal eyes, the brain can learn the meaning of the signals and, in effect, see. Using this material as an artificial eye for both human and robot application will be possible.

Phthalocyanine is a biomimetic molecule that has properties similar in some respects to bacterial rhodopsin. It is a photosensitive porphyrin-like dye. When placed in a lipid membrane together with other compounds, it shows photo effects. As with other photosensitive materials that are reversible, it could be useful for molecular electronic applications.

Self-Assembly Systems, Data Fusion Arrays, and Characterization of the Sensor Surface

Most recent approaches have focused on exploiting the interaction of binding molecules with the surface of the sensor to construct sensors and provide quality control in the production of sensors. Techniques with sensitivities that can be applied to this problem include, in part, Atomic Force Microscopy (AFM), optical tweezers, membrane micropipette manipulations, and manipulation of functionalized magnetic beads by magnetic force fields. All these approaches have evolved toward methods used in analyzing molecular interactions that are most suitable for interrogating the interactions of a single molecule. AFM has been used to measure individual molecular interactions by separately modifying the surfaces of the AFM probe and the target surface with complementary binding agents. Using atomic force microscopes and Nearfield Optical Scanning Microscopy (NSOM) will be possible to quality control microscale and nanoscale fabrication. As an example, avidin passively adsorbed to the surface of the AFM probe was used to scan the surface that was derivatized with biotin. The rapid association of avidin with biotin was observed as the two surfaces came into closer contact and eventually touched. On retracting the AFM probe from the biotin-coated surface, the force fluctuations between the avidin and the biotin could be measured. The AFM system allows structural defects in thin films to be recognized at Angstrom-level resolution.

The speed at which the AFM probe pulls away from the substrate significantly affects the force that is needed to rupture the receptor-ligand complex. Direct measurements of the forces between complementary strands of DNA were measured by AFM, where sample DNA was bound to the AFM probe and substrate surfaces by complementary capture of oligonucleotides. For nucleic acid detection of DNA or RNA sequences in samples where these analytes are in the range of 100–1,000,000 copies, some form of amplification is required.

ADDITIONAL DATA

Tables 3.2-1A and 3.2-1B present additional data on this developing critical technology area.

Table 3.2-1A. Biological Sensors Militarily Critical Technologies

Technology	Developing Critical Technology Parameter	Critical Materials	Unique Test, Production, and Inspection Equipment
Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Section 4, Biomedical Technology)	The gene sequence codes of PAIs; determine epitopes specific for AG BW agents.	Complimentary DNA sequence or epitope/ Gke surface.	None identified.
Biosensors for odors/light/sound/pressure	Chemical to electron/ phonon transduction; pressure to electron/ phonon transduction. Incorporate sensor in thin film; MEMS. Design sensor surface to accommodate attachment of molecular recognition elements (10^4 per pixel) in a functionally active state.	Host transducing materials.	None identified.
Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Section 4, Biomedical Technology)	The gene sequence codes of PAIs; determine epitopes specific for AG BW agents.	Complimentary DNA sequence or epitope/ Gke surface.	None identified.
Biosensors for odors/light/sound/pressure	Chemical to electron/ phonon transduction; pressure to electron/ phonon transduction. Incorporate sensor in thin film; MEMS. Design sensor surface to accommodate attachment of molecular recognition elements (10^4 per pixel) in a functionally active state.	Host transducing materials.	None identified.

Table 3.2-1B. Biological Sensors Militarily Critical Technologies

Technology	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Section 4, Biomedical Technology)	Database of PAIs and cell surface markers.	Medical/ pharmaceutical food industries lead.	Clinical detection of infectious agents; food processing.	Biomedical and food industry lead military applications.	Ready access.	None identified.
Biosensors for odors/light/sound/ pressure	Algorithm of chemical light/ sound or pattern unique to targets.	Food industry, chemical processing; military.	Food spoilage; toxicant release.	Military and food industries can have similar impact on technology.	Ready access.	None identified.
Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Section 4, Biomedical Technology)	Database of PAIs and cell surface markers.	Medical/ pharmaceutical food industries lead.	Clinical detection of infectious agents; food processing.	Biomedical and food industry lead military applications.	Ready access.	None identified.
Biosensors for odors/light/sound/ pressure	Algorithm of chemical light/ sound or pattern unique to targets.	Food industry, chemical processing; military.	Food spoilage; toxicant release.	Military and food industries can have similar impact on technology.	Ready access.	None identified.

SECTION 3.3—BIOMATERIALS AND NANOFABRICATION

Highlights

- Miniaturization at the nanometer-scale level will facilitate high-density information storage, retrieval, and processing.
- Biomaterial-based circuit and switching devices will be available on the nanometer scale to enable rapid and accurate responses to changing requirements for applications of military force.

OVERVIEW

The rapid progress in biochemistry and molecular biology has provided industry with many new classes of materials. These include structural materials (silks and bioceramics, such as chitins); electron/photon conductive polymers, such as cytochrome and polyporphyrins; and ion gating molecules, including bioreceptors (adhesives from barnacles that can function on wet surfaces); and lubricants that are biocompatible. Because many biomaterials can self-assemble, these materials have been used to pattern sensor surfaces having thicknesses in the nanometer range. The biomaterials are produced in living organisms. The cost of production is modest, requiring only fermentation-like facilities. Because the living cells replicate, small starter cultures can be used to produce large numbers of organisms. The living organisms require aqueous systems for growth and, therefore, are environmentally advantageous. Organic solvent requirements are minimized, thereby reducing remediation, treatment, and pollution costs. The technology of genetic engineering permits proteins synthesized in one order or species of animal to be synthesized in other organisms. By this method, proteins normally made only in mammals, including humans, can be produced on a large scale in bacteria, yeast, or plants. One form of such engineering involves the use of cassette mutation, most studied in yeast. Cassette mutation allows entire genes of interest to be inserted into a microorganism for large-scale manufacture of the gene product.

The following subareas are critical to increasing military superiority and advanced economic competitiveness:

- **Nanofabrication.** Fabrication of miniaturized electronic and photonic switches, circuits, and molecular motors
- **Biomaterials.** Production of high-tensile-strength, low-weight materials.

Biopolymer-based systems have specificity and selectivity with regard to the chemical processes they facilitate. A major advantage of biosystems is their self-assembly properties. Such self-assembly occurs at the nanometer scale. The materials provide opportunities in the manufacture of artificial retinas, microsensor chips, and electron/phonon switching devices. These technologies provide large numbers of lightweight sensors that operate in ambient temperatures.

TECHNOLOGY DESCRIPTIONS

Nanofabrication

Biomaterials, such as proteins, lipids, nucleic acids, can self-assemble. Self-assembly is the formation of organized, patterned structures without external direction. The fidelity of the self-assembly is extraordinarily high. These self-assembled components can be complex and perform unique functions. An example of self-assembly is the formation of pores by the addition of hemolysin from Staph. aureus to a solution containing lipid membranes. The proteins will join together and form a pore in the membrane without any external manipulation. Other examples include the appropriate folding of proteins as they are synthesized from messenger RNA and the assembly of a biomolecular motor that consists entirely of proteins (dynein and kinesin) combined in such a fashion that the product is an engine. Many polymers can self-assemble into membrane-like structures. Examples are the formation

of monolayer of alkylthiols on gold surfaces, silanes on glass and metal oxides, and organic molecules into polymers on conducting surfaces by electropolymerization.

Within the next 5–15 years, using self-assembling techniques to produce nanosize gears, motors, and other mechanical and electronic components in the nanometer size range will be possible. Such devices will find application in monitoring human health, behavior, and the environment. They may even be capable of assembling within the body by simple addition in "monomeric form." These devices will perform functions presently requiring complex, expensive, and proportionally large integrated circuitry. They can also perform tasks not related to humans.

Using Microelectromechanical Systems (MEMS) technology and possibly self-assembly and nanofabrication, producing small devices capable of switching will be possible. These devices may be used to change wavelength in optical systems, turn electronic devices or circuits on and off, or monitor specific phenomenon in systems, the environment, or the human body. The ability to change wavelength can lead to low-weight iconographic presentation formats on helmet mounted displays (HMDs).

Atomic Force Microscopy (AFM) and Nearfield Scanning Optical Microscopy (NSOM) use a technique that involves maintaining close contact between a cantilevered probe and a surface by maintaining either constant potential, resistance or other measurable quality. The device produces a "picture" of surfaces at the molecular level. This picture can be the physical surface, the electrical potential, the resistance, the magnetic differences, or several other qualities that this surface may possess. In all these cases, the device produces a diagram of that surface or that surface property at the molecular level.

In the next decade, the devices will be available in a hardened and portable form. With portable devices, examining surfaces in our external environment for changes, contaminants, or other characteristics that may have commercial or military application will be possible. One possible example of a commercial application would be the production of silicon or diamond chips for integrated circuits. Using atomic force microscopes and NSOM, quality control microscale and nanoscale fabrication can be realized. Such a device on a production line would be extremely useful in looking for defects if it could be designed to scan surfaces at a relatively rapid rate.

Biomaterials

Within a decade, scalable, artificial imagers with optical response functions that more closely resemble human retinal response will be developed. These artificial imagers will be scalable to large sizes, will be low cost, and will have on-chip image processing functions. The materials include amorphous Silicon (a-Si) thin-film transistor (TFT) imaging arrays in conjunction with photosensitive layers comprised of materials such as bacteriorhodopsin (bR). Bacteriorhodopsin has the unique attribute that the generated photo response of a bR film yields the integral characteristic of the incident optical image. This means that the bR layer generates a photovoltage whose magnitude is proportional to the time rate of change of the incident optical signal. Thus, an imaging system with bR as the photosensitive layer performs optical processing functions that lead to systems that respond as edge or motion detectors. Combined with more conventional imager response functions, these bR-based imagers can yield a better picture of remote battlefield conditions. In addition, fabricating imagers with pixels that use the orientation properties of bR films is possible. By fabricating individual pixels with regions that exhibit opposite orientation, generating optical response functions that closely mimic the response of retinal ganglion cells is possible. Such cells have particular sensitivity to moving or stationary target tracking. These are required elements of smart targeting weapons. These imagers could replace traditional sensor elements for strike, night vision, or reconnaissance missions.

Lightweight, chemical-resistant, shrapnel-resistant, self-cooling materials are under development, using biological systems as models. The ceramic coatings of insects and shellfish are metal-protein-carbohydrate complexes. Spider silk, plant tassle silk, and silkworm silk all have high strength-to-mass ratios. These materials may be readily modified because proteins and carbohydrates contain many functional groups for grafting other materials. This ease of grafting has advantages in attachment of sensors to the clothing fabric.

Signature reduction of a soldier may be achieved using a uniform made from a polymer material with side chains of a chiral material that reduces his signature to radar. A material that will reduce the infrared (IR) signature of a soldier at night is also very likely within the next 5–10 years—if it not already available.

ADDITIONAL DATA

Tables 3.3-1A and 3.3-1B present additional data on this developing critical technology area.

Table 3.3-1A. Biomaterials and Nanofabrication Militarily Critical Technologies

Technology	Developing Critical Technology Parameter	Critical Materials	Unique Test, Production, and Inspection Equipment
Smart biomaterials	Optimize match or contrast color of cloth to environment (e.g., electroactive polymers, bioceramics, HMD).	None identified.	None identified.
Self assembly biomaterials	Production of nanometer-scale materials (midterm).	Contractile proteins that self assemble.	None identified.

Table 3.3-1B. Biomaterials and Nanofabrication Militarily Critical Technologies

Technology	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
Smart biomaterials	Algorithm for matching tuned materials to environment.	Primarily military.	Structural integrity of materials that become deformed.	None identified.	Limited.	None identified.
Self assembly biomaterials	None identified.	Medicine; manufacturing.	Nanometer-scale motors; microfluidics.	None identified.	Ready access.	None identified.

SECTION 3.4—INDIVIDUAL AND GROUP PROTECTION

Highlights

- Novel biomaterials will enable reinsertion of military persons into active service at a rate several times faster than current techniques.
- Performance indicators will enable timely and appropriate intervention and maintain readiness and fitness assessment.
- Pharmaceuticals and performance enhancers will protect the combat force from endemic disease and extend mission performance capability.
- Biological tests will decrease combat morbidity and mortality by a factor several times faster than existing techniques.
- Prompt protection of human systems through analysis and assessment of food, water, and environmental factors will reduce the occurrence of disabling human disease and increase capability in a fighting force with fewer combatants.

OVERVIEW

New insights regarding the molecular mechanisms involved in pathogenicity have given rise to countermeasures that may be employed if people are exposed to infectious diseases or agents. During the next two decades, novel material developments will provide filters that bind and inactivate biological agents, with minimal reduction of air flow, thereby protecting people. Telecommunications and the development of haptic devices are key to the introduction of remote surgical procedures that medical corpsmen can perform under the guidance of surgeons located at a distance. These methods of telemedicine have applications in the training of physicians and in the delivery of medicine to people residing in less densely populated areas. This innovation is important because early effective treatment of trauma provides higher survival rates.

Biotechnology advances have also provided insights into the molecular basis of immune protection, vascular fluid loss, and neural regeneration. Enhanced immune competency permits forces to function at maximal strength after deployment. Sick calls are normally a problem during the first few weeks after deployment. Enhancement of the immune response by vaccination with super-antigens, by treatment with biological response modifiers, or by food additives may ameliorate the problem. Extensive fluid loss is a primary cause of loss of life from traumatic injury. Applications of newly developed compatible blood clotting biopolymers, administered intra-abdominally to stanch blood loss, will help to ensure survivability. Spinal cord injuries constitute a major cause of long-term disability because current techniques do not permit regeneration of severed Central Nervous System (CNS) connections. New techniques, using growth factors and biocompatible guidance materials, are being developed to facilitate regrowth and repair of the CNS.

The following subareas are critical to increasing individual and group protection and survivability:

- Biomedical imaging and transporting pods
- Encapsulation
- Pathogen genome project and pathogenicity islands (PAIs)
- Biocompatible blood substitutes and clotting matrices

Remote locator of persons to permit rescue of captured personnel

- Water purification
- Biomarkers for toxicant/stress exposure.

Enhanced prophylaxis can be achieved by using active vaccination against endemic infectious agents. Vaccination with super-antigens or advanced adjuvants (i.e., improved antigen presentation) can upregulate the immune system before deployment and provide protection in a 4-day period rather than the usual 10-day post vaccination period. The enabling technologies include genomic sequencing of all known and infectious disease organisms; multi-component, multi-valent vaccination systems to upregulate the immune system; and the development of immune response modifiers, including interferons and interleukins, having the potential to enhance immune response. The sequencing of pathogenicity islands can reduce the total number of vaccines needed.

New technologies that protect people before deployment include DNA vaccines. These vaccines have become available as an additional technology to the current vaccine systems that have eliminated small pox and controlled childhood diseases.

New sets of antibiotics that inactivate pathogenicity islands may have utility in individual and group protection. These antibiotics can be anti-sense materials or chemicals similar to traditional antibiotics. Developing antibiotics that have not been used to eliminate the development of drug resistance in the general population is important.

TECHNOLOGY DESCRIPTIONS

Biological Imaging and Transporting Pods

Pod-like units that permit patients who have been exposed to biological organisms to be transferred to remote sites have been built.

The pod is a bi-directional system that reports the personal information and also receives information about the environment, allowing the individual to take the appropriate action. This does not necessarily require individual-level monitoring if the device can be electronically linked to a nearby area monitor or sensor. The pod can encapsulate a patient in a small, automated decontamination (DECON) pod that can be managed by a crew smaller than that needed to encapsulate a large DECON team.

Encapsulation

Many biologically active materials lose activity when exposed to oxidizing environments or to dilution in aqueous environments. Encapsulation of the biologically active material in a variety of matrices (e.g., liposomes, lactides, hydrogels) stabilizes the biomaterials and can provide a delivery vehicle for slow release. The slow release can be activated by enzymes normally found in the body or by pulsed electromagnetic signals. The release is a function of the chemical nature of the encapsulating material. Encapsulation can also provide targeted delivery of the biologically active material to specific organs if the capsules are coated with antibodies, lectins, or polycations. Encapsulation technology has potential applications in delivering taggants for a variety of applications.

Pathogen Genome Project and Pathogenicity Islands

The entire genome of many pathogenic organisms has been determined. As a result, the genomic sequences responsible for increased virulence and PAIs of these organisms have been characterized. It is apparent that the number of PAIs is smaller than the number of organisms because the same PAIs are shared by several organisms. This observation can lead to the development of new antibiotics and anti-sense technologies to reduce virulence.

Biocompatible Blood Substitutes and Clotting Matrices

Polymers having oxygen-carrying capabilities are available. Many of these are fluorinated compounds but have a disadvantage of showing hepatotoxicity. Biopolymeric oxygen-carrying compounds and clot-inducing compounds are being developed with anticipated product availability in the 2005 time period. These new products should have universal acceptor compatibility and not require human donors.

Remote Locator of Persons To Permit Rescue of Captured Personnel

Compounds may be developed that, when metabolized, will result in the excretion of compounds that are strong chromophores. Operators must be able to turn on or off. The signal generator can be placed internally so it cannot "easily" be removed. The device will be low cost and contain a physiological "honesty" checker so if "scared" Johnny cuts his finger, he will not activate unnecessarily and draw needed assets. The system may be used to locate a sailor overboard.

Water Purification

Current technology requires use of reverse osmosis (RO). Desalinization of sea water and purification of contaminated water can be achieved using a combination of filtration and RO. New technologies that are effective in defouling and regenerating the capillary tubes in the RO system are being developed.

Transgenic flora and fauna are being developed to produce for renewable resources (water, food, therapeutics). Microbes capable of bioremediation and terraforming terrain to shape the environment are being examined.

Biomarkers for Toxicant/Stress Exposure

Humans and other animals, when challenged with fever, infection, or emotional stress, synthesize a variety of biological compounds. The synthesized compounds may be of low molecular weight (e.g., adrenalin) or high molecular weight (e.g., acute phase proteins, glutathione transferases, cytochrome P 450). Exposure of individuals to stress, exhaustion, or other adverse conditions also results in changes in electrophysiological and behavioral characteristics of the affected people. The changes in the profiles of body chemicals, electrophysiological patterns, and behavior may be used as signatures to evaluate fitness and readiness.

ADDITIONAL DATA

Tables 3.4-1A and 3.4-1B present additional data on this developing critical technology area.

Table 3.4-1A. Individual and Group Protection Militarily Critical Technologies

Technology	Developing Critical Technology Parameter	Critical Materials	Unique Test, Production, and Inspection Equipment
Encapsulation	Release of chemical or biological response modifiers on demand (near term).	Encapsulation vehicles that stabilize biochemicals and release high percentage of active biological (greater than 80 percent).	None identified.
Novel anti-virals and antibiotics (see Section 4, Biomedical Technology)	Intervene in infectious entry into target, infection of secondary organ systems; replication in cells and release of infectious particles; (near term to mid term).	Anti-virals and novel antibiotics.	None identified.
Organ culture; tissue growth (see Section 4, Biomedical Technology)	Replace organs (midterm).	Production of organ stem cells and organs that are accepted in immune-competent people.	None identified.
Temperature and biotic system controlled transport pods	Development of pod that can stanch bleedings, have sterile environment, and contain B agents (midterm).	Materials suitable for filtration, body covering, weight bearing, shock absorbing, and humidity control.	None identified.

Table 3.4-1B. Individual and Group Protection Militarily Critical Technologies

Technology	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
Encapsulation	None identified.	Biomedical, pharmaceutical; cosmetics; drug delivery.	Biomedical, pharmaceu-tical; cosmetics; drug delivery.	Drug delivery; vaccination.	Ready access.	None identified.
Novel antivirals and antibiotics (see Section 4, Biomedical Technology)	None identified.	Biomedical and pharmaceutical industry and food industry.	Biomedical and pharma-ceutical industry and food industry.	Health, food quality.	Ready access.	None identified.
Organ culture; tissue growth (see Section 4, Biomedical Technology)	None identified.	Health care dominates.	Health care; pharmaceu-tical production.	Medical organ replacement.	Ready access.	None identified.
Temperature and biotic system controlled transport pods	Vital sign monitor.	Primarily military; emergency preparedness teams in isolated locations.	Biomedical.	Rural medical emergencies and preparedness tasks.	Ready access.	None identified.